REMARKS

Claims 109-120 are pending. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

DETAILED ACTION

Claim Rejections under 35 U.S.C. § 103

1. The Examiner has rejected claims 109-120 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Alexion's press release dated January 6, 2003 in view of Collard (Arterioscler Thromb Vasc Biol. [1999] 19(11): 2623-29). The Examiner alleges that Alexion's press release teaches the use of the anti-C5 antibody, eculizumab, for the treatment of subjects with paroxysmal nocturnal hemoglobinuria (PNH). The Examiner alleges that treatment of NO deficiency in PNH patients would be an inherent property of eculizumab. The Examiner states that the press release does not specifically link the hemolytic disease with NO deficiency or the effect of h5G1.1-scFv on NO levels. The Examiner alleges, "Collard teaches the treatment of hypoxic HUVECs with h5G1.1-scFv. Collard teaches that terminal complement component C5b-9 deposition results in a functional loss of NO-dependent relaxation, increases VCAM-1 expression and decreases cGMP levels. Collard teaches that decreased cGMP levels may compromise vascular blood flow because of decreased endothelium-dependent relaxation and increased adhesion of neutrophils to the endothelium. Collard teaches that h5G1.1-scFv treatment of the HUVECs attenuates C5b-9 deposition and preserves acetylcholine induced increases in cGMP after hypoxia/reoxygenation." The Examiner alleges it would have been obvious to use h5G1.1-scFv antibody for the treatment of NO deficiency in a subject. The Examiner further argues that the claims are drawn to a genus of conditions involving NO deficiency and that the teachings of the combined references are drawn to a species of NO deficiency. Applicants respectfully traverse.

The claims are drawn to methods for treating ***nitric oxide (NO) deficiency*** in a subject by administering a compound to the subject, which compound: (i) binds to one or more complement components, (ii) blocks the generation of one or more complement components, or (iii) blocks the activity of one or more complement components.

The Press Release relates to the efficacy of an anti-C5 antibody, eculizumab, in treating patients with the hemolytic disease paroxysmal nocturnal hemoglobinuria (PNH). As acknowledged by the

Examiner, the Press Release "is silent about the treatment of NO deficiency in paroxysmal nocturnal hemoglobinuria." (See Office Action at page 2.) Moreover, the Press Release does not disclose or even suggest that NO deficiency is associated with hemolysis or the desirability of using eculizumab to treat NO deficiency. The Examiner acknowledges this fact by stating that "the Alexion press release ***does not specifically link*** the hemolytic disease with NO deficiency or the effect of h5G1.1-scFv on NO levels." (See Office Action at page 2; emphasis added.) The Examiner relies on Collard to provide at least one of these essential links.

Collard is a research article disclosing the results of *in vitro* experiments related to the effect of C5b-9 deposition on re-oxygenated human umbilical vein endothelial cells (HUVEC), and the ability of an anti-C5 antibody to prevent the C5b-9 deposition. However, Collard does not disclose or even suggest hemolysis or any hemolytic disease, let alone PNH – the focus of the Press Release. Furthermore, the reference is silent on NO deficiency, methods for treating NO deficiency, and the desirability of using an anti-C5 antibody (or any other compound embraced by the claims) to treat NO deficiency in any subject, let alone the patients described in the Press Release. There simply would have been no reason for the skilled artisan reading the Press Release to turn to a scientific article that does not relate to hemolysis, hemolytic diseases, PNH, or NO deficiency, and thus arrive at the claimed invention. Thus, Collard does not establish the required link between hemolytic disease and NO deficiency as alleged by the Examiner.

The Examiner also argues that Collard links the effect of h5G1.1-scFv on NO levels. The basis for this argument appears to be the Examiner's contention that the skilled artisan would have been motivated to practice the claimed methods "by the showing of Alexion that h5G1.1-scFv antibody [sic][1] treatment of PNH relieved hemolysis and the teachings of Collard that C5b-9 deposition during reoxygenation after a hypoxic event inhibited NO-mediated cGMP expression[.]" (See Office Action at page 3.) However, Applicant respectfully points out first that the experiments described in Collard relate to the use of an anti-C5 antibody to modulate the effect of C5b-9 deposition on ***acetylcholine (ACh)***-mediated cGMP production, not "NO-mediated cGMP expression" as stated in the Office Action. (See Collard at page 2625, "Effect of Complement on Endothelial cGMP.")

[1] As first noted in Applicant's Response dated June 23, 2008, Applicant again points out that *eculizumab* is h5G1.1-mAb, rather than h5G1.1-svFv as the Examiner states. h5G1.1-scFv is in fact the single chain antibody named *pexelizumab*.

Notwithstanding this consideration, Applicant also reminds the Examiner that the subject claims are drawn to methods for treating ***NO deficiency*** in a subject, not methods for "relieving inhibition of NO-mediated cGMP expression." While Collard may disclose, e.g., that "deposition of C5b-9 on vascular endothelium results in a functional loss of NO-dependent relaxation," the reference does not disclose or even suggest that C5b-9 deposition on HUVEC, or any other cells, has an effect on ***NO levels*** (e.g., NO concentration, NO production, or NO metabolism).

As noted in Applicant's Response dated June 23, 2008, the loss of NO-dependent relaxation referred to in Collard is neither functionally nor temporally equivalent to ***NO deficiency***. For example, NO deficiency results in a host of pathological conditions – e.g., reduced clot dissolution and significant fibrin deposition and thrombus formation – that do not involve the NO-mediated cGMP signaling events discussed in Collard. (See, e.g., Rother et al. (2005) *JAMA* 293(13): page 1658, center column; of record.) Moreover, NO deficiency would precede any downstream effects that NO has on the cGMP-dependent relaxation processes discussed in Collard. Thus, the skilled artisan would have had no reason to expect that the methods described in Collard would be useful for treating an upstream event like ***NO deficiency***. Therefore, not only does Collard fail to establish a link between hemolytic disease and NO deficiency, but it also fails to link the effect of h5G1.1-scFv on NO levels, as required of the arguments set forth in the Office Action.

Furthermore, to negate the patentability of the claimed invention, the cited combination of references must teach or suggest each and every element of the claimed invention. The deficiencies of the press release are not remedied by the teachings of Collard. Collard does not disclose that ***NO deficiency*** can be treated with complement inhibitors as claimed in the present application. Relieving a functional loss of NO-dependent relaxation does not teach or suggest treatment of NO deficiency. Functional loss of NO-dependent relaxation is not equivalent to NO deficiency as the latter occurs upstream of the decreased cGMP signaling shown in Collard. One of ordinary skill in the art would not expect the teachings of Collard to relieve symptoms of NO deficiency not associated with decreased cGMP signaling. The instant claims are specific to ***NO deficiency*** and do not encompass functional loss of NO-dependent relaxation when there is not NO deficiency. Therefore, the functional loss of NO-dependent relaxation disclosed in the cited references is not a species of the instant claims as the Examiner asserts and is not sufficient to render the claims obvious.

In summary, Applicant respectfully submits that neither the Press Release nor Collard, alone or combination, render the claims obvious. Moreover, there would have been no reason for the skilled

artisan to combine the two references and arrive at the claimed methods and the references fail to teach or suggest each and every element of the claimed invention. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. If an additional fee is due, please charge our Deposit Account No. 18-1945, under Order No. **ALXN-P01-114** from which the undersigned is authorized to draw.

Dated: February 20, 2009

Respectfully submitted,

By _____

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